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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/060,697	01/30/2002	Donald W. Petersen	06317-038003	8553

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EXAMINER
WITZ, JEAN C

ART UNIT	PAPER NUMBER
1651	

DATE MAILED: 07/02/2002 4

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/060,697	PETERSEN, DONALD W.	
	Examiner	Art Unit	
	Jean C. Witz	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15-30* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15-30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 16-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of O'Leary et al. (5,484,601), Yim et al. and WO 9840113 taken as a whole.

Claim 16 recites a bone graft substitute composition comprising calcium sulfate, a mixing solution, a plasticizing substance, cancellous bone and demineralized bone matrix. Dependent claims specify the amounts of the components and recite specific substances that are used for the calcium sulfate component, the mixing solution component and the plasticizing substance component. The specification discloses that the object of the invention is to create a bone graft substitute composition that has "extended set time and sufficient robustness to withstand fluid impact with minimal erosion for expanded clinical application." Applicants also state that other objects of the invention is to "provide a bone graft substitute composition that can be mixed into a paste and then loaded into a syringe and ejected for an extended period of time (e.g., more than ten minutes)" and to "provide a bone graft substitute composition that can be mixed into a putty and then handled and formed into desired shapes for an extended period of time (e.g., more than ten minutes)."

O'Leary et al. disclose a flowable demineralized bone matrix composition for use in bone repair. O'Leary et al. state at col. 1, lines 36-43 that "[I]t is a particular object of the invention to provide a composition of liquid or pastelike consistency comprising demineralized osteogenic bone powder and a biocompatible liquid synthetic organic material as a carrier for the bone powder with or without such optional ingredients as thixotropic agents, medicaments, and the like, and to apply the composition at a bone defect site to induce new bone ingrowth at the site." At col. 3, lines 14-20, the patent states "[t]o provide the demineralized allogeneic bone powder composition of this invention, the demineralized bone powder with or without any of the foregoing optional components mentioned above absorbed therein is combined with a biocompatible liquid synthetic organic material which functions as a carrier or suspension agent for the bone powder." The patent further defines the terms "liquid" and "flowable" as "intended to include (1) organic materials which in the pure or highly concentrated state and at ambient temperature, e.g., 15-40° C. are flowable liquids and (2) organic materials which in the pure or concentrated state and at ambient temperature are normally solid but dissolved in a suitable solvent, e.g., water or a biocompatible organic solvent such as ethanol, can be provided in liquid form. Functionally, the liquid component of the composition serves to provide a flowable material of widely varying consistency. The term "flowable" as used herein applies to compositions whose consistencies range from those which can be described as shape-sustaining but readily deformable, e.g., those which behave like putty, to those which are runny. Specific forms of flowable bone powder compositions include cakes, pastes, creams

and fillers." O'Leary et al. disclose at col. 3, line 56 to col. 4, line 6 that "[w]here, in a particular bone powder composition, the bone powder has a tendency to quickly or prematurely separate from the carrier or to otherwise settle out from the composition such that application of a fairly homogeneous composition is rendered difficult or inconvenient, it can be advantageous to include within the composition a substance whose thixotropic characteristics prevent or reduce this tendency. Thus, e.g., where the carrier component is glycerol and separation of bone powder occurs to an excessive extent where a particular application is concerned, a thickener such as a solution of polyvinyl alcohol, polyvinylpyrrolidone, cellulosic ester such as hydroxypropyl methylcellulose, carboxy methylcellulose, pectin, food-grade texturizing agent, gelatin, dextran, collagen, starch, hydrolyzed polyacrylonitrile, hydrolyzed polyacrylamide, polyelectrolyte such as polyacrylic acid salt, etc., can be combined with the carrier in an amount sufficient to significantly improve the suspension-keeping characteristics of the composition. Finally, O'Leary et al. disclose at col. 2, line 53 to col. 3, line 13, that "[a]ny of a variety of substances can be introduced into the bone particles" and includes a non-limiting list which includes inorganic elements, parenchymal cells, growth factors, bone morphogenic proteins, and mesenchymal elements.

Therefore, O'Leary et al. provides the motivation to produce a bone graft substitute composition containing a mixing solution, a plasticizing substance consistent with those described in the specification and demineralized bone matrix. Further limitations of the claims are also disclosed by the patent. For example, the claims

requires the presence of 10-100 parts by weight of demineralized bone matrix. O'Leary et al. teach at col. 4, lines 18-22 that "[t]he amount of bone powder which can be incorporated into the composition of this invention can vary widely with amounts of from about 5 to about 80 weight percent, and preferably from about 20 to about 60 weight percent, being entirely suitable in most cases." That which the specification defines as a "plasticizing substance" (cellulosic esters such as hydroxypropyl methylcellulose and carboxy methylcellulose) are identified as included in the composition of O'Leary as a thixotropic agent.

While there is no explicit disclosure of the presence of calcium sulfate or cancellous bone, it is noted that the O'Leary patent clearly teaches that "any variety of substances" can be introduced to the composition include "inorganic elements".

Yim et al. discloses a composition for delivery of osteogenic proteins for the purpose of promoting the growth of bone at the site of the delivery of the proteins. The patent states that "the subject invention involves pharmaceutical formulations designed to sequester osteogenic protein in situ for a time sufficient to allow the protein to induce cartilage and/or bone formation." Yim et al. teach that "[o]steogenic proteins are those proteins capable of inducing, or assisting in the induction of, cartilage and/or bone formation. Many such osteogenic proteins have in recent years been isolated and characterized, and some have been produced by recombinant methods. For example, so-called bone morphogenic proteins (BMP) have been isolated from demineralized bone tissue." Yim et al. further teach that "[I]n U.S. Pat. No. 5,171,579, it is disclosed that osteogenic proteins can be sequestered at a site

where bone inducing activity is desired using autogenous blood, without using antifibrinolytic agents, provided that a porous particulate polymer matrix is incorporated into the formulation. To reduce the preparation time and improve the above formulation's handling characteristics, [Patentees] have surprisingly found that it is desirable to add a calcium sulfate hemihydrate-containing substance (CSHS). The CSHS is preferably either pure calcium sulfate hemihydrate, also known as Plaster of Paris (POP), or a mixture of POP and hydroxyapatite (POP:HA). Adding a CSHS reduces setup time and provides improved moldability and consistency of the resulting formulation.

Yim et al. state that the osteogenic proteins can be utilized in the form of a pharmaceutically acceptable solution and cites sodium chloride as an appropriate solubilizing agent, as well as multiple different aqueous solutions of amino acids and other acids. See col. 3, line 53. Further, at col. 4, lines 32-33, the osteogenic protein formulations may be lyophilized and reconstituted with water prior to use. Yim et al. also include a "porous particulate polymer matrix component" that acts as an "in situ scaffolding for the osteogenic protein, while having biodegradable properties allowing for replacement by new bone growth" as well as a "protein-sequestering material". This material is used to "hold" the osteogenic proteins at the site for a sufficient time to allow them to have a bone growth promoting effect. This may be a blood clot from autogenous blood. Yim et al. states that "[i]n the absence of such blood clot, osteogenic protein desorbs from the [particulate polymer matrix] particles in situ at a rate such that the osteoinducing effect of the protein is not clinically significant."

Suitable "protein-sequestering agents" are disclosed at col. 7, lines 25-34, as cellulosic materials such as alkylcelluloses (including hydroxyalkylcelluloses), such as methylcellulose, ethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropyl-methylcellulose, and carboxymethylcellulose." The cellulosic protein sequestering agent is preferably present in a concentration of about 2 to about 10% (w/v). Determination of the quantity of the calcium sulfate hemihydrate is disclosed as being well within the skill of the practitioner and is determined to be that quantity which provides the best handling properties both immediately after and 1 to 2 hours after preparation will be optimal. The formulations of the disclosure of Yim et al. provide "malleable implants that allow therapeutically effective amounts of osteoinductive protein to be delivered to an injury site where cartilage and/or bone formation is desired. Such an implant may be used as a substitute for autologous bone graft in fresh and non-union fractures, spinal fusions, and bone defect repair in the orthopaedic field; in cranio/maxillofacial reconstructions; for prosthesis integration, especially as a surface coating to improve fixation of prosthetic implants such as hydroxylapatite coated prostheses; in osteomyelitis for bone regeneration; and in the dental field for augmentation of the alveolar ridge and periodontal defects and tooth extraction sockets. When used to treat osteomyelitis or for bone repair with minimal infection, the osteogenic protein may be used in combination with porous microparticles and antibiotics, with the addition of protein sequestering agents such as alginate, cellulosics, especially carboxymethylcellulose, diluted using aqueous glycerol." The patent further states that "[t]he lower viscosity formulations may also be used as a

percutaneous injection to accelerate healing of closed fractures. In certain of these uses, the compositions of the subject invention may be used in combination with various bone cements, including erodible bone cements such as poly(propylene-co-fumarate) and certain hydroxyapatite cements. Also, certain of these uses will utilize bioerodible hardware such as erodible plates, screws, etc. As alluded to above, the dosage regimen will be determined by the clinical indication being addressed, as well as by various patient variables (e.g. weight, age, sex) and clinical presentation (e.g. extent of injury, site of injury, etc.). In general, the dosage of osteogenic protein will be in the range of from about 10 to 1000 μg, preferably from about 10 to 100 μg."

Therefore, Yim et al. provides the disclosure of a bone graft substitute composition, similar to O'Leary et al., which contains calcium sulfate, a mixing solution, and a plasticizing substance and which has improved moldability and consistency. The bone morphogenic proteins of the Yim reference, while not identical in composition to demineralized bone matrix of the claims, serves the same purpose, i.e. the delivery of bone growth promoting proteins to a site of bone injury. As noted previously, bone morphogenic proteins are present in demineralized bone matrix, and are obtained via extraction of demineralized bone matrix. Further limitations of the claims are also disclosed by the patent. For example, the claims require specific mixing solutions. Yim et al. discloses, in a non-limiting list, both water and sodium chloride as a solvent present in the composition for the osteogenic proteins. Since calcium sulfate hemihydrate (plaster of paris) requires an aqueous solution to activate it and allow it to harden, one of ordinary skill in the art would be aware such a solution would be

necessary and the selection of either sterile water or saline or other buffers is deemed conventional and well within the skill of the practitioner. To that end, it is noted that the patent to Yim et al. clearly acknowledges that a composition containing calcium sulfate hemihydrate must be kept dry until the time of its use since the addition of an aqueous solution causes the activation of the calcium sulfate hemihydrate and results in ultimate hardening of the calcium sulfate hemihydrate (such as seen with the use of plaster of paris). Yim et al. state at col. 8 that "[t]he osteogenic protein and porous particles of the formulations may be provided to the clinic as a single vial formulation, either as a solution or in lyophilized form, or the formulation may be provided as a multicomponent kit wherein, e.g. the osteogenic protein is provided in one vial and the porous particles and calcium sulfate hemihydrate-containing substance each are provided in separate vials." Further, Yim et al. discloses the mixing of the osteogenic proteins in solution with the calcium sulfate hemihydrate. The aqueous solvent of the osteogenic proteins, such as water or sodium chloride, would be expected to activate the calcium sulfate hemihydrate. When including the calcium sulfate hemihydrate component into the composition of O'Leary et al., one of ordinary skill in the art would be aware and motivated to provide an aqueous activating mixing solution since the bone morphogenic proteins are contained within the dry demineralized bone matrix .

The claims also require the presence of approximately 1 to 40 parts of the plasticizing substance by weight. Yim et al. teaches at col. 7, lines 40-45, that the cellulosic protein sequestering agent is preferably present in 2-10% (w/v). The claims define the specific cellulose derivatives. Plasticizing substances such as recited in the

claims are identified as included in the composition of Yim et al. as a protein sequestering agent.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the composition of O'Leary et al. with components of the composition of Yim et al. Both O'Leary et al. and Yim et al. have the same object in creating a malleable, workable bone growth promoting composition. One of ordinary skill in the art when reviewing the disclosure of Yim would have been motivated to include a calcium sulfate component into the composition of O'Leary et al. with the expected benefit disclosed by Yim et al., i.e. that a calcium sulfate component would add improved handling, moldibility and consistency to the formulation of O'Leary as well as reducing the set up time. The compositions of Yim and O'Leary are so sufficiently similar that one of ordinary skill in the art at the time the invention was made would be aware of the properties of the calcium sulfate hemihydrate would not impair or otherwise negatively affect the components of the O'Leary composition. Both compositions contain components that provide either directly or indirectly osteogenic proteins, and both compositions contain a cellulosic material which is being used for the same purpose, i.e. to impart viscosity and suspension properties to the respective compositions. The general amounts of both the demineralized bone matrix and the cellulose material are taught by the references. The optimization of the amount of calcium sulfate and mixing solution to be further included is deemed well within the skill of the practitioner at the time the invention was made as it is clear that the amount of calcium sulfate is directly related to desired rate of set up of the composition, i.e. the

more calcium sulfate used, the faster the composition will set up and harden. Further, it is clear that the amount of mixing solution is inversely related to the desired set up time and directly proportional to the ultimate consistency of the composition, i.e. the more mixing solution used, the more dilute the calcium sulfate and the slower the set up time but the more liquid the composition will become.

Finally, the claims recite the further inclusion of cancellous bone. Both patents teach that other conventional components included in bone growth promoting compositions may be included in the disclosed compositions. The disclosure of WO 9840113 is also drawn to a bone paste for the repair of bone defects. The disclosed paste contains demineralized bone matrix, an inorganic component such as ceramics hydroxyapaptite and calcined bone, or bone morphogenic proteins or other growth factors and mixtures thereof. Other ingredients which may be present in the paste include wetting agents and carboxymethyl cellulose (see pages 5-6). At page 13, the reference states that the composition "may act as a carrier for cortical, cancellous or cortical and cancellous bone chips. Such compositions are useful for filling larger bone voids. In addition, when these bone chips are not demineralized, they provide an added spectrum of biological properties not exhibited by the gelatin alone or the gelatin plus the osteogenic components (i-iv)."

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to include cancellous bone chips into the composition of O'Leary et al. for the benefit described in the disclosure of WO 9840113, i.e. they fill

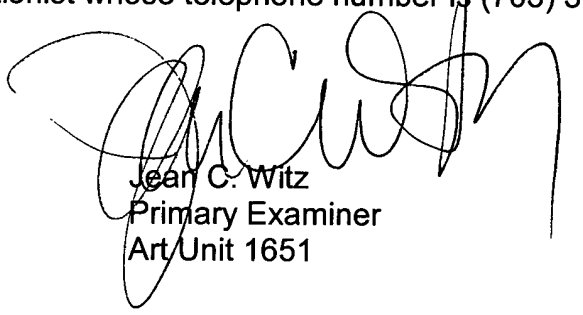
larger bone voies and provide an added spectrum of biological properties to the composition.

It is clear that the components as claimed are all well known to be included in bone graft compositions. It is clear that there is a benefit to the formulation of the composition as a moldable composition. The prior art clearly indicates that plasticizing substances such as are claimed are known to be used in prior art moldable bone graft compositions expressly for the purpose of improving the moldability of the composition. It is also clear that demineralized bone matrix is conventionally included in a moldable bone graft composition for the purpose of acting as an osteoinductive agent by delivering bone morphogenic proteins to the area of the desired bone graft. It is also clear that the addition of calcium sulfate hemihydrate, an inorganic compound that becomes moldable when wetted and then ultimately hardens, is both well known and imparts another beneficial property to moldable bone grafts such that the grafts are moldable when inserted into the desired area but harden in that area such that they are not washed away by body fluids nor expressed or moved by body motion. Finally, it is clear that it is conventional to include cancellous bone chips into moldable bone graft compositions for the benefit of both osteo-induction and as a large bone void filler. Applicants are claiming conventional bone graft composition ingredients combined in a conventional manner and in known amounts. Further, the state of the art of these components are so well known that optimization of amounts for the purpose of changing the both the flowable and "set-up time" properties of the composition are deemed well within the skill of the practitioner.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Jean C. Witz
Primary Examiner
Art Unit 1651

June 28, 2002